ORIGINAL ARTICLE

Exenatide improves cisplatin induced ovarian damage through NLRP3, Nrf-2, and TLR4 pathways

La exenatida mejora el daño ovárico inducido por cisplatino a través de las vías NLRP3, Nrf-2 y TLR4

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Abstract

Objective: *Cisplatin (CP) toxicity causes ovarian damage by oxidative stress, inflammation and fibrosis. The aim of the present study is to investigate the possible beneficial effects of exenatide on the experimental ovarian damage model produced by CP.* **Method:** *For 14 rats, CP was administered by intraperitoneally (i.p) twice a week for 5 weeks. No drug was administered to the remainder of rats (n = 7) (Group 0). The rats taken CP were divided into two groups. Group 1 rats (n = 7) were given 1 mL/kg/day saline i.p., and Group 2 rats (n = 7) was given with 20 μg/kg/day exenatide.* **Results:** *The number of primordial, primary, secondary, and tertiary follicle was significantly lower in Group1 compared with Group 0 and Group 2. The ovarian fibrosis percent was significantly higher in Group 1 than Group 0 and 2. The plasma anti-Mullerian hormone value was lower in Group1compared with Group 0 and 2. Over Nuclear factor-erythroid factor 2-related factor 2 level, Over Toll-like receptor 4 level and over nucleotide-binding domain leucine-rich repeat and pyrin domain containing receptor 3 were higher in Group 1 compared with Group 0 and 2.* **Conclusion:** *exenatide has possible beneficial effect on ovarian damage induced by CP by anti-inflammatory actions and can be a promising candidate for ovarian damage caused by CP.*

Keywords: *Cisplatin. Exenatide. Ovarian. Toxicity.*

Resumen

Objetivo: *La toxicidad del cisplatino causa daño ovárico por estrés oxidativo, inflamación y fibrosis. El objetivo del presente estudio fue investigar los posibles efectos beneficiosos de la exenatida en el modelo experimental de daño ovárico producido por el cisplatino.* **Método:** *A 14 ratas se les administró cisplatino por vía intraperitoneal (i.p.) dos veces por semana durante 5 semanas. No se administró fármaco al resto de la ratas (n = 7, grupo 0). Las ratas que recibieron cisplatino se dividieron en dos grupos. Las ratas del grupo 1 (n = 7) recibieron 1 ml/kg/día de solución salina i.p. y las ratas del grupo 2 (n = 7) recibieron 20 μg/kg/día de exenatida.* **Resultados:** *El número de folículos primordiales, primarios, secundarios y terciarios, fue significativamente menor en el grupo 1 en comparación con los grupos 0 y 2. El nivel superior a NrF2, el nivel superior a TLR-4 y el nivel superior a NLRP-3 fueron más altos en el grupo 1 en comparación con los grupos 0 y 2.* **Conclusión:** *La exenatida tiene un posible efecto beneficioso sobre el daño ovárico inducido por el cisplatino por acciones antiinflamatorias, y puede ser un agente candidato prometedor para el daño ovárico causado por el cisplatino.*

***Palabras clave*:** *Cisplatino. Exenatida. Ovario. Toxicidad.*

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Introduction

In 1978, the food and drug administration (FDA) authorized the use of cisplatin (CP) (cis-diamminedichloroplatinum [II]) as a chemotherapeutic agent and it is a widely used for a wide range of solid tumors[1]. Dose-dependent toxicity is one of the most significant obstacles to CP treatment[2], CP-induced ovarian damage in women of reproductive age is an important problem.

CP therapy causes injury to the ovary of experimental animals and 70% of animals treated with CP are sterile[3,4]. The most widely accepted mechanisms of CP toxicity10 are the production of reactive oxygen species (ROS) and the onset of oxidative stress. CP also increased the levels of proinflammatory cytokines in ovarian tissue[4]. Therefore, antioxidative and anti-inflammatory drugs may be beneficial for treating oxidative and inflammatory ovarian damage caused by CP-induced infertility.

The FDA approved exenatide, a peptide with similar physiological effects to glucagon-like peptide 1 (GLP-1) but a prolonged half-life, as a new type of hypoglycemic medication in 2005. GLP-1 was found to have vascular protection, neuroprotection, and anti-inflammatory properties[5,6]. Furthermore, GLP-1 and its analogs (such as exenatide) have been studied for the treatment of liver, kidney, and lung fibrosis[7-10].

The GLP-1 analogs are considered important in terms of their antitumor properties and their ability to prevent chemotherapy-cytostatic drug-induced injury to normal tissue[11]. Furthermore, exenatide was found to reduce ovarian and endometrial damage in streptozocin-induced diabetic rats[12].

The aim of the present study is to investigate the possible beneficial effects of exenatide in CP-induced experimental ovarian damage model.

Method

Animals

Twenty-one adult female Wistar rats, weighing 200-210 g, were used in the study. The experiments performed in this study have been carried out according to the rules in the Guide for the Care and Use of Laboratory Animals adopted by National Institutes of Health (U.S.A). Having received Animal Ethics Committee's consent (University, Ethical number: 17210316). The rats used in the experiment were obtained from Experimental Animal laboratory of Science University. Rats were fed ad libitum and housed impairs in steel cages having a temperature-controlled environment (22 ± 2°C) with 12-h light/dark cycles[13].

Experimental protocol

For 14 rats, CP (Sisplatin, Kocak Pharma) (2 mg/kg/day) was administered by intraperitoneally (i.p) twice a week for 5 weeks (total CP dose 20 mg/kg). No drug was administered to the remainder of rats (n = 7) (Group 0). The rats taken CP were divided into two groups. Group 1 rats (n = 7) were given 1 mL/kg/day 0.9% NaCl (saline) i.p., and Group 2 rats (n = 7) was given with 20 μg/kg/day Exenatide (Byetta, Lilly, 0.25 mg/mL) were administrated by i.p. every day for 5 weeks.

At the end of the study, all animals were sacrificed (cervical dislocation) with ketamine (100 mg/kg, Ketasol, Richterpharma AG Austria)/xylazine (50 mg/kg, Rompun, Bayer, Germany) anesthesia, and their blood samples were collected by cardiac puncture for biochemical analysis. Their ovaries were removed for histological and biochemical examinations[13].

Histological examination

Ovarian tissues were formalin-preserved and embedded in paraffin. The ovaries were sectioned at a thickness of 4 μm with a microtome. The sections were then stained with hematoxylin and eosin and mounted onto glass slides. All sections were photographed with an Olympus C-5050 digital camera mounted on an Olympus BX51 microscope. Histopathological examination of the ovaries was performed by a computerized image analysis system (Image-Pro Express 1.4.5, Media Cybernetics, Inc., Rockville, MD, USA) on ten microscopic fields per section at a magnification of ×20, performed by an observer who was blinded to the study groups. Primary follicles consist of an oocyte surrounded by a single layer of cuboidal granulosa cells. Secondary follicles include multiple layers of cuboidal granulosa cells and an invisible antrum. Tertiary follicles are characterized by a stratum granulosum along with fluid-filled antral space. Stromal fibrosis in ovarian tissue was calculated as a percentage[13].

Measurement of plasma anti-mullerian hormone (AMH) levels

Blood was centrifuged at 3000 rpm for 10 min at room temperature and stored at −20°C until the analysis for

AMH. AMH level was measured using commercially available enzyme-linked immunosorbent assay (ELISA) kits (Biosciences, Seattle, WA, USA). Samples from each rat were determined in duplicate according to the manufacturer's guide.

Determination of lipid peroxidation

Lipid peroxidation was determined in plasma samples through measuring malondialdehyde (MDA) levels as thiobarbituric acid reactive substances (TBARS), which are the end product of lipid peroxidation. Trichloroacetic acid and TBARS reagent were added to the tissue samples, then mixed and incubated at 100°C for 60 min. The samples were centrifuged at 3000 rpm for 20 min, and the absorbance of the supernatant was read at 535 nm after cooling on ice. MDA levels of tissue were calculated from the calibration curve using 1,1,3,3-tetraethoxypropane and expressed as nmol/gr protein.

Over tissue biochemical analysis

After sacrification, over were rapidly removed and stored at –20°C until to biochemical analysis. For tissue analysis, tissues were homogenized with a glass homogenizer in 5 vol of phosphate buffered saline (Ph, 7.4) and centrifuged at 5000 g for 15 min. Nuclear factor-erythroid factor 2-related factor 2 (Nrf-2), Toll-like receptor 4 (TLR-4), nucleotide-binding domain leucine-rich repeat (NLR) and pyrin domain containing receptor 3 (NLRP-3) level in the tissue supernatants were measured using commercially available rat ELISA kits. All samples from each animal were measured in duplicate according to the manufacturer's guidelines. A microplate reader was used for the measurement of the Absorbances (MultiscanGo, Thermo Fisher Scientific Laboratory Equipment, NH, US)[14].

Statistical analysis

Data analysis was performed using GraphPad Prism 8.3.0 a software (GraphPad Software, La Jolla, CA, USA). The groups of parametric variables (biochemical data) were compared by student's t-test and analysis of variance. The groups of non-parametric variables (histopathology) were compared by the Mann–Whitney U test. Results are presented as the mean ± standard error of mean. A value of $p < 0.05$ was accepted as statistically significant. $p < 0.001$ was accepted as statistically highly significant.

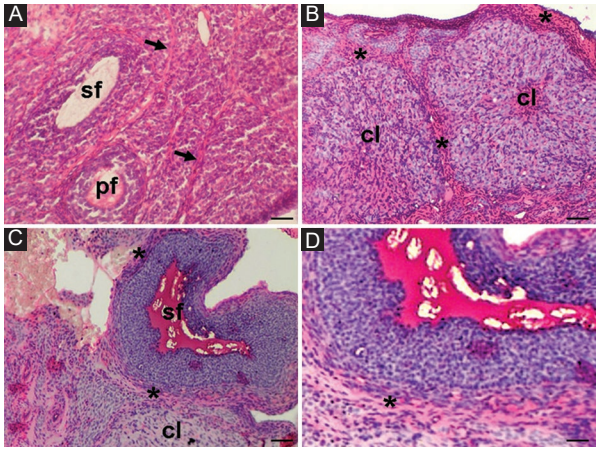

Figure 1. *Histopathological examination of ovaries. Hematoxylin and eosin stain.* **A:** *normal Control group of ovaries with normal morphology, normal stroma of ovary (arrow) (hematoxylin and eosin, ×10 magnification).* **B:** *cisplatin+saline group with stromal fibrosis of the ovary (asterisk).* **C:** *cisplatin+Exenatide group demonstrating significant decrease of stromal fibrosis of the ovarian tissue (asterisk) (×10 magnification).* **D:** *cisplatin +Exenatide group, reduction of stromal fibrosis appears to be better in higher magnification (hematoxylin and eosin, ×40 magnification). pf: Primary follicle sf: secondary follicle, cl: corpus luteum.*

Results

The number of primordial follicles was significantly lower in Group 1 compared with Group 0 and Group 2 ($p < 0.001$ and $p < 0.01$, respectively). The number of primary follicles was significantly higher in Group 2 and group 0 compared with Group 1 ($p < 0.01$ and $p < 0.01$, respectively). The secondary follicle number was found to be significantly lower in Group 1 compared with Group 0 and Group 2 ($p < 0.01$ and $p < 0.01$, respectively). Tertiary follicle number was also significantly lower in Group 1 compared with Group 0 and Groups 2 ($p < 0.01$ and $p < 0.01$, respectively). The ovarian fibrosis percent was significantly higher in Group 1 than Group 0 and Group 2 ($p < 0.001$ and $p < 0.001$, respectively) (Fig. 1 and Table 1).

The plasma AMH value was lower in Group 1 compared with Group 0 and Group 2 ($p < 0.01$ and $p < 0.01$, respectively). The plasma MDA level was found to as significantly higher in Group 1 compared with Group 0 and Group 2 ($p < 0.0001$ and $p < 0.01$, respectively). Over NrF2 level was higher in Group 1 than Group 0 and Group 2 ($p < 0.001$ and $p < 0.01$, respectively). Over TLR-4 level was found as significantly higher in Group 1 compared with Group 0 and Group 2 ($p < 0.0001$ and $p < 0.01$, respectively). Over NLRP-3 level was significantly higher in Group 1 than Group 0 and Group 2 ($p < 0.0001$ and $p < 0.001$, respectively) (Table 2).

Discussion

The main finding of the present study is the beneficial effects of the GLP-1 agonist exenatide on CP-damaged ovarian tissue. These advantages include the preservation of primordial, primary, secondary, and tertiary follicular pools as well as the amelioration of ovarian fibrosis.

CP-induced ovarian toxicity is an important for women of reproductive age[15,16]. CP suppresses mitosis[17] in tumor cells by cross-linking their DNA. CP is lethal to healthy cells due to increased ROS production[4,18]. Increased production of proinflammatory cytokines such TNF-, IL-1, and IL-6 also leads to non-tumor cell death[4,18]. The NF-kB pathway is activated as proinflammatory cytokines increase. The suppressed NF-kB-Ikb complex in the cytoplasm becomes active and translocate to the nucleus with proinflammatory cytokines, where it promotes target genes and initiates inflammatory events[19]. Damage caused by inflammation causes lipid peroxidation and increases MDA release.

AMH is produced by ovarian granulosa cells and could indicate ovarian reserve[20]. Menopause reduces AMH[21,22]. AMH protects primordial and preantral follicles[23,24]. Follicle degeneration and apoptosis diminish ovarian reserve and AMH levels[24]. The CP and saline group showed lower primordial and preantral follicle counts, as well as serum AMH, than the control and CP and exenatide groups. Exenatide appears to decrease follicular degeneration detected by lower AMH levels in rodents exposed to CP.

NLRP3 is a member of the inflammasome protein family[25]. Hereditary Cryopyrin-associated periodic syndrome has been connected to the NLRP3 gene. NLRP3 inhibitors have been used to treat these diseases[26]. However, little is known about the effects of NLRP3 on ovarian tissue. Recent research indicates that the NLRP3 inhibitor MCC950 is effective in treating ovarian endometriosis increasing the functionality of endometriotic ovaries[27]. Exenatide, was shown to[28] inhibit the inflammasome pathway in rodents and decrease oxidative stress[29] in an experimental model of nonalcoholic fatty liver disease. In the current study, the CP and saline groups had significantly higher levels of NLRP3 than the control group and the CP and exenatide group. Exenatide appears to prevent CP-induced damage to the ovary by inhibiting the NLRP3 pathway.

Nrf-2 is the primary regulator of oxidative status in numerous tissues. It is believed that Nrf-2 regulates catalase, thioredoxins, glutathione, glutathione reductase, and other antioxidants[30]. Agents that enhance Nrf-2 activity have been utilized for the control of oxidative stress in several neurological diseases. Nrf-2 inhibitors are also used to increase oxidative stress in tumor tissues. In the present investigation, the highest Nrf-2 levels were found in the CP and saline groups. We believe that this increase was due to the oxidative damage induced by CP exposure. In addition, the serum MDA level, a sensitive indicator of oxidative stress in tissue, was found to be higher in the CP and saline group compared to the control and CP and exenatide

Table 1. Comparisons ovarian stromal degeneration, ovarian follicle degeneration and ovarian stromal fibrosis scores between groups

Variables	Normal control group	Cisplatin and saline group	Cisplatin and exenatide group
Primordial follicle	15.1 ± 0.9	4.5 ± 0.8*	11.4 ± 1.7##
Primary follicle	13.4 ± 2.5	6.7 ± 0.6*	9.1 ± 0.9#
Secondary follicle	11.5 ± 0.6	5.4 ± 0.3*	8.3 ± 0.2#
Tertiary follicle	3.9 ± 0.1	1.7 ± 0.2	2.6 ± 0.3#
Ovarian fibrosis percent (%)	2.2 ± 0.3	15.1 ± 1.4**	7.5 ± 3.06##

Results were presented as mean ± standard error of mean. Statistical analyses were performed by one- way analysis of variance.
*p < 0.01.
**p < 0.0001 different from normal groups.
#p < 0.01.
##p < 0.001.

Table 2. Comparisons Plasma AMH level, Plasma MDA level, Over NrF2 level, Over TLR-4 level and Over NLRP-3 level between groups

Variables	Normal control group	Cisplatin and saline group	Cisplatin and exenatide group
Plasma AMH (ng/mL) level	2.9 ± 0.18	0.6 ± 0.09*	1.1 ± 0.15#
Plasma MDA level (nM)	45.6 ± 7.5	131.7 ± 14.2**	68.4 ± 5.09#
Over NrF2 level (pg/mg)	415.4 ± 22.7	747.1 ± 34.5*	621.3 ± 19.6#
Over TLR-4 level (ng/mg)	5.08 ± 0.4	16.1 ± 1.8**	9.4 ± 1.05#
Over NLRP-3 level (pg/mg)	32.9 ± 4.4	89.8 ± 6.5**	57.7 ± 8.1##

Results were presented as mean ± standard error of mean. Statistical analyses were performed by one- way analysis of variance.
*p < 0.01.
**p < 0.0001 different from normal groups.
#p < 0.01.
##p < 0.001.
AMH: anti-müllerian hormone; MDA: malondialdehyde; NrF2: Nuclear factor-erythroid factor 2-related factor 2; NLRP-3: nucleotide-binding domain leucine-rich repeat (NLR) and pyrin domain containing receptor 3; TLR: Toll-like receptor.

groups. In previous studies[12,31,32], exenatide was shown to reduce oxidative stress. On ovarian tissue damaged by CP, exenatide can act as an antioxidant system activator.

TLR4 is an essential component of the host's innate immune system. There is evidence linking TLR4 to the development and progression of cancer[33]. TLR4[33] has been shown to modulate several cytokines, including IL-1b, IL-6, and TNF-. TLRs are presented in numerous tissues, including the ovary. Various ovarian cells, including cumulus, granulosa, and theca cells, contain TLRs[34]. Exenatide decreased the expression of TLR4 and other inflammatory markers in diabetic patients, according to Chaudhuri and colleagues[35]. In this study, we found that the CP and saline groups had significantly increased ovarian TLR4 levels than the other groups. We believe that the rapid anti-inflammatory effect of exenatide improved ovarian injury.

This is the first study to demonstrate the beneficial effects of exenatide on CP-induced ovarian injury. Pathways NLRP3, Nrf-2, and TLR4 can connect the potential mechanisms. Exenatide can contribute to the reversal of CP-induced damage to ovarian tissue and is a promising candidate for women who have experienced CP-induced ovarian damage.

Conclusion

Present study is the first to demonstrate beneficial effects of exenatide on ovarian damage which was induced by cisplatin. The possible mechanisms can be related via NLRP3, Nrf-2 and TLR4 pathways. Exenatide can lead reverse the damage of cisplatin on ovarian tissue and can be promising candidate for women who had ovarian damage by cisplatin damage.

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Conflicts of interest

The authors declare no conflicts of interest.

Ethical considerations

Protection of humans and animals. The authors declare that the procedures followed complied with the ethical standards of the responsible human experimentation committee and adhered to the World Medical Association and the Declaration of Helsinki. The procedures were approved by the institutional Ethics Committee.

Confidentiality, informed consent, and ethical approval. The study does not involve patient personal data nor requires ethical approval. The SAGER guidelines do not apply.

Declaration on the use of artificial intelligence. The authors declare that no generative artificial intelligence was used in the writing of this manuscript.

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